CASE REPORT

Durable Complete Remission of PD-L1 Positive NUT Carcinoma Treated With Concurrent Chemotherapy and Radiation

Minggui Pan, MD, PhD1,2; James S Chang, MD1

INTRODUCTION

NUT carcinoma is a rare disease with only several dozen cases reported in the literature, and associated with very aggressive course with approximately 6 to 9 months of median life expectancy.1 The largest case report from the literature was a collection of 54 cases with outcome result available that showed 1- and 2-year progression-free survival was 15% and 9%, and 1- and 2-year overall survival of 30% and 19%.2,3 The disease is characterized by the somatic fusion of BRD4 and NUT gene in approximately 75% of cases (BRD3 and other variants in the rest of the cases).4 The fusion gene leads to overexpression of c-Myc that blocks the epithelial differentiation, which likely plays a central role in its oncogenic development.5 Here we share our experiences with 2 patients who obtained durable complete remission (CR) after treatment with concurrent chemotherapy and radiation, using 2 completely different chemotherapy regimens.

CASE REPORT

Case 1

Patient is a 31-year-old man who presented in May 2019 with approximately 3-month history of increasing cough, night sweats, shortness of breath, chest pain, and weight loss of 35 lb. Computed tomography and positron emission tomography (PET) scans showed extensive mediastinal masses extending to the neck (Figure 1, left). No disease outside of neck and mediastinum was present. He underwent ultrasound-guided biopsy of a neck mass that revealed NUT carcinoma with squamous cell differentiation and strong immunostaining of NUT protein in a strong, diffuse, and speckled pattern of nuclear reaction in nearly all the tumor cells (performed at Stanford University Department of Pathology). Molecular profiling using StratanaNGS (Ann Arbor, MI) revealed BRD4-NUTM1 fusion and low tumor mutation burden (TMB). Immunostaining showed PD-L1 expression in 2% of tumor cells with 1+ to 2+ intensity (by NeoGenomics, Fort Myer, FL). Patient was in excellent health before this illness and had no significant family history of cancer. The laboratory workup was negative for HIV and hepatitis B and C. In June 2019, he initiated chemotherapy with VAC (vincristine, Adriamycin, and cyclophosphamide, based on the protocol for Ewing sarcoma) with rapid symptomatic improvement. Three weeks after this 1 cycle of VAC chemotherapy, he started concurrent chemotherapy and radiation with IE (ifosfamide 1000 mg/m² and etoposide 60 mg/m² day 1 to 5 and day 29 to 34). He received a total of 6000 cGy of external beam radiation in 30 fractions. Two weeks after he completed radiation, a PET scan showed complete resolution of all the fludeoxyglucose (FDG) uptakes of the mediastinal and neck masses as well as marked reduction of the tumor size (Figure 1, right). Patient continued to receive chemotherapy with 2 additional cycles of VAC and 2 additional cycles of IE (ifosfamide 1800 mg/m² and etoposide 100 mg/m² for 5 days) in alternating manner, before he discontinued chemotherapy because of increasing toxicities (severe fatigue and weakness). A PET scan again showed no abnormal FDG uptake approximately 18 months after the diagnosis and the initiation of treatment.

Case 2

Patient is a 70-year-old woman who presented in April 2018 with several weeks of left neck and shoulder pain. A PET scan showed avid FDG uptake of a mediastinal mass that measured approximately 6.2 × 6.0 × 4.3 cm with pleural effusion but no evidence of extrathoracic disease (Figure 2, left). Biopsy of the mass by thoracic surgeon revealed NUT carcinoma with...
strong nuclear staining of NUT protein in a diffuse and speckled pattern in most of the tumor cells. Molecular testing with StrataNGS showed BRD3-NUTM1 fusion gene and low TMB. Interestingly, immunostaining performed by NeoGenomics showed that the tumor expressed PD-L1 100% 3+. A repeat PET scan approximately 2 months later immediately before the initiation of treatment showed that the mediastinal mass had grown to 10 × 8.4 × 6.5 × cm. In September 2018, patient underwent concurrent chemotherapy and radiation with weekly carboplatin and paclitaxel for 6 weeks and total of 6000 cGy external beam radiation in 30 fractions (1000 cGy was given as boost). Because of worsening performance status, patient skipped week 5 but resumed week 6 chemotherapy. Repeat PET scan approximately 2 months after completion of chemoradiation showed partial response with decreased size (approximately 7.5 × 6.1 × 5.2 cm) and FDG uptake. Gradual shrinkage of the mediastinal mass was seen on subsequent serial PET scans. Approximately 13 months after the initiation of treatment, PET scan revealed complete resolution of the FDG uptake of the left mediastinal mass with shrinkage to a size of 2.4 × 1.5 cm that appeared consistent with radiation scarring. PET scan continued to show CR 21 months after the initiation of treatment (Figure 2).

CONCLUSION

NUT carcinoma is extremely rare and difficult to treat with dismal prognosis. For resectable disease, surgery is performed first, followed by chemotherapy and/or radiation. For unresectable disease, treatment includes chemotherapy and radiation. The chemotherapy regimens reported in the literature vary from case to case and there is no standard protocol available. A couple of bromodomain and extra-terminal motif inhibitors have been developed and given as compassionate use for patients with NUT carcinoma, but their efficacy is unclear. We have reported 2 patients here whose disease was unresectable, received concurrent chemotherapy and radiation, and have remained in CR for 21 months after the diagnosis and the initiation of therapy. Completely different chemotherapy regimens were used in the 2 patients with concurrent radiation. The first case presented with severe symptoms and extremely large tumor burden that infiltrated the entire mediastinum and achieved CR soon after concurrent chemotherapy and radiation was completed. Patient received additional intense chemotherapy with IE and VAC regimens based on the protocol for Ewing sarcoma. The use of this regimen in NUT carcinoma has not been reported in the literature and can well be an effective protocol for patients with high tumor burden. The second case presented with lower tumor burden and obtained CR 13 months after the completion of treatment with concurrent chemotherapy and radiation without additional chemotherapy and has remained in CR for 21 months now. The tumor shrinkage and resolution of FDG uptake occurred over time in a gradual fashion, very different from the first case. Both patients had positive PD-L1 expression and low TMB. In an abstract with 9 patients reported by Rooper et al., 4 patients had PD-L1 expression (mean expression 17%) and were associated with better survival compared with the 5 patients without PD-L1 expression. The outcomes of our 2 patients appear to support the notion that positive PD-L1 expression may be associated with better survival and indicates that immune checkpoint inhibitor may be an viable option if the patient develops relapsed disease.

In conclusion, our experiences with these 2 successfully treated patients can be helpful for the management of NUT carcinoma to achieve optimal outcome. The patient with extremely high mediastinal tumor burden treated with concurrent chemoradiation and radiation using ifosfamide and etoposide regimen may be a more effective protocol than the other regimens that have been reported in the literature. PD-L1 expression should be examined in all patients with NUT carcinoma given its potential prognostic and therapeutic implications.

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

Authors’ Contributions

Durable Complete Remission of PD-L1 Positive NUT Carcinoma Treated With Concurrent Chemotherapy and Radiation

James S. Chang. Final approval of manuscript: All authors. Accountable for all aspects of work: All authors

Funding statement
This study was supported by Kaiser Permanente.

How to Cite this Article

References